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Clinical Research in Practice: The Journal of Team Hippocrates

Volume 2 | Issue 1 Article 9

2016

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Recommended Citation

Bolig T. Glucocorticoids do not decrease mortality in severe alcoholic hepatitis. *Clin. Res. Pract.* June 1, 2016;2(1):eP1087. doi: 10.22237/crp/1464790318

Clinical Research in Practice
The Journal of Team Hippocrates
VOL 2 ISS 1 / eP1087 / JUNE 1, 2016

Glucocorticoids do not decrease mortality in severe alcoholic hepatitis

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ABSTRACT A critical appraisal and clinical application of Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med*. 2015;372(17):1619-28. doi: 10.1056/NEJMoa1412278

Keywords: glucocorticoids, steroids, prednisolone, alcoholic hepatitis, liver failure, STOPAH trial

Clinical Context

A 31-year-old female with no significant past medical history presented with acute, severe alcoholic hepatitis after a weekend of heavy binge drinking. The patient was icteric and encephalopathic at the time of presentation and was started on lactulose and rifaximin. Her serum total bilirubin was 7.6. The Maddrey's discriminant score was calculated and found to be 32.9—a significant finding as a Maddrey score of ≥ 32 is associated with a mortality rate of 30% within the first 28 days.[1] Given the high Maddrey's discriminant function and the acute presentation, the question was raised if the patient should be started on a steroid. The efficacy of glucocorticoid use to decrease mortality in severe alcoholic hepatitis has been a topic of debate for decades. Glucocorticoid use is not without side effects to the patient (e.g. risk of infection), so an investigation of the literature was conducted.

Clinical Question

Do glucocorticoids decrease mortality in patients with severe alcoholic hepatitis?

Research Article

Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med*. 2015;372(17):1619-28. doi: 10.1056/NEJMoa1412278

Literature Review

A Pubmed/MEDLINE and Google Scholar search was conducted for "glucocorticoid use in severe alcoholic hepatitis". A number of meta-analyses, review articles, and randomized control trials comment on this topic. More recent review articles like "Pharmacotherapy for alcoholic patients with alcoholic liver disease" note that glucocorticoids and pentoxifylline show promise, but the only successful method of liver protection in alcoholic hepatitis currently recommended is avoidance of alcohol and symptomatic treatment.[2] Meta-analyses are equivocal in regard to steroid use in this clinical scenario. A systematic review and network meta-analysis in Gastroenterology demonstrates a benefit from corticosteroids alone or in combination with pentoxifylline at 28 days but no benefit in medium term survival (3-12 months).[3] The most recent (2008) Cochrane systematic review on this topic

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ISSN: 2379-4550
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VOL 2 ISS 1 / eP1087 / JUNE 1, 2016

showed no significant decrease in mortality of steroids vs placebo/no treatment, commented on the heterogeneity of studies, and recommended the need for larger, low-bias placebo-controlled studies.[4]

The focus of the search was on randomized control trials related to steroid use and if it decreased mortality. Studies such as the Ramond paper in NEJM have helped establish the use of steroids in severe alcoholic hepatitis for the previous two decades.[5] This and other studies had sample sizes that were smaller than the STOPAH trial (i.e. the appraised article). Also, inclusion criteria were broader—hepatic encephalopathy alone was an inclusion criterion, and some patients with more chronic liver disease were not excluded from some studies. Earlier RCTs on the topic often used biopsy-proven alcoholic hepatitis. Due to this, treatments were initiated later and is not a scenario equivalent to clinical practice (i.e. wouldn't wait for biopsy to start patient in hospital). Finally, some of these older studies only looked at short-term outcomes and had limited long-term follow-up when compared to the STOPAH trial.

The research article for this appraisal was chosen despite that in the title one can see that it is comparing prednisolone to pentoxifylline.[6] This was a multicenter, randomized control trial in the New England Journal of Medicine with a large cohort of patients. The therapies were compared to one another, in combination, and against a placebo (4 groups). The population studied fits the patient and her clinical scenario most closely (overall younger patient age, no liver biopsy-more related to clinical practice).

Critical Appraisal

This article describes a randomized, double-blind trial with controls that has a CEBM evidence level of 1b. The primary end point of this RCT was mortality at 28 days and secondary endpoints were mortality or transplant at 90 days and one year. The patient population included in this study were patients with a clinical diagnosis of alcoholic hepatitis. The patients had to be 18 years or older, consume an average minimum amount of alcohol daily (80 g for men, 60 g for women), a minimum serum bilirubin (4.7 mg/dL), and a discriminant score of at least 32. These are very reasonable inclusion criteria and are consistent with a clinical diagnosis. The research team decided not to design a study that confirmed alcoholic hepatitis by biopsy. This was a wise decision on the part of the researchers because they wanted to have the study closely match the clinical scenario in which therapy would be initiated. This is with the caveat that some patients may be included with another or concomitant underlying liver pathology. However, the exclusion criterion of presence of other causes of liver disease in addition to the physician's clinical judgement should minimize this. The rest of the exclusion criteria were abstinence of alcohol consumption two months before the randomization, previous jaundice for more than 3 months, extremely elevated hepatocellular enzymes (ALT>300; AST>500), and previous inclusion in a study. These criteria help solidify the diagnosis of alcoholic hepatitis in selected patients. Each patient received standard supportive and nutritional care. Patients with renal failure, active GI bleeding, sepsis, and those requiring inotropes were not excluded if these conditions stabilized within first 7 days of admission. In previous studies, patients with these conditions, especially any GI bleeds, were excluded. Including these patients makes this study much more applicable to the clinical setting. The article makes it a point to note that inclusion of these patients did not have an effect on the overall mortality.

The patients were randomized by software and stratified by risk (high-risk group included those with GI bleed, renal impairment, or sepsis; all other patients were intermediate risk) and by geography using a block size of four. The trial had 1026 patients enrolled, which in general is a much larger sample size than previous trials. The authors did acknowledge having a funding issue that did not allow them to analyze 33 patients who underwent randomization during the last 90 days and 159 patients who underwent randomization with 90 days to 12 months. Fifty patients were lost to follow up for the primary outcome, allowing for the planned intention-to-treat analysis with acceptable validity. This helps eliminate attrition bias, which may be seen in this patient population.

Looking at the end point of mortality at 28 days, 17% of the placebo group had died, and 14% of patients died who were in the prednisolone group. The odds ratio of prednisolone therapy was 0.72 (95% CI 0.52-1.01) with a p-value of 0.06. This did not reach significance but approached it. A secondary analysis was performed using a multivariate logistic-regression model taking into account determinants of prognosis and found that prednisolone significantly decreased morality at the 28 day period. The OR was 0.61 (95% CI of 0.41-0.91; p=0.02). However, no secondary statistical modeling has the validity of the primary pre-specified outcome measures, so this information should be used cautiously.

Although the null hypothesis was not rejected, further studies into glucocorticoid therapy are warranted. It is important to note, however, that the prednisolone group did see a statistically significant increase in rate of infection when compared to placebo (13%

ISSN: 2379-4550
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vs 7% p=0.002). Therefore, a 28 course of prednisolone did not show a statistically significant decrease in mortality at the end of 28 days and had a statistically significant higher incidence of infection. This higher incidence of infection did not affect mortality, since there was no difference in mortality outcomes at 90 days and one year.

Clinical Application

Although steroid therapy for severe alcoholic hepatitis has been used for treatment, recent studies have suggested that it may not be effective in decreasing mortality. This is what spurred the literature review to answer this clinical question. In fact, steroid therapy was not started in this patient. The hepatology department was consulted for this case, and their view was consistent with this clinical appraisal. They had already stopped the practice of glucocorticoids in severe alcoholic hepatitis despite the most current guidelines which still recommend 40mg prednisolone/d for 28 day course with two week taper.[1,6,7]

Given the evidence in the article prednisolone therapy may not be wanted by a patient. A physician would have to describe steroid therapy as only possibly providing benefit with an increased risk of infection. The discussion with the patient should also include that after the 28-day mark there is still a high incidence of mortality after the acute phase (i.e. 90 days and 1 year), and that abstinence from alcohol is a necessity because it is currently the only recommended method to protect hepatocytes in patients with alcoholic liver disease.[2]

Lessons:
1.) Clinical decision making can be a difficult task when studies are equivocal.
2.) Just because therapies have been used for long periods of time, does not mean they shouldn't be questioned by evidence-based practice.
3.) Professional association guidelines may be outdated. In-service specialists are a valuable resource.

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